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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/963,990 | 09/26/2001 | George P. Livi | P51176 | 3345 |

7590 06/18/2003

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| EXAMINER |
|---|
| PARAS JR, PETER |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

DATE MAILED: 06/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application N . | Applicant(s) | |
|---|---|---|---|
| | 09/963,990 | LIVI ET AL. | |
| | Examiner | Art Unit | |
| | Peter Paras, Jr. | 1632 | |

*-- The MAILING DATE f this communicati n app ars on the cover sheet with the corresp ndenc address --*

**Period f r Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *01 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *4-11,13 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

Claims 1-14 are pending.

### *Election/Restrictions*

Applicant's election with traverse of Group 12, claims 1-3 and 12, in Paper No. 5 is acknowledged. The traversal is on the ground(s) that there may be phenotypic overlap between the various transgenic *C. elegans* embraced by the claims. Upon consideration of Applicant's arguments, the Examiner hereby withdraws the restriction requirement with respect to Groups 1-25.

The remainder of the restriction requirement with respect to Groups 26-58 is maintained for the reasons of record set forth in the restriction requirement of 1/31/03. Applicants have not provided any arguments traversing the restriction of Groups 26-58.

Accordingly, the requirement with respect to Groups 26-58 (as originally numbered in the restriction requirement of 1/31/03) is still deemed proper and is therefore made FINAL.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 4-11 and 13-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no

allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 5.

### *Specification*

The disclosure is objected to because of the following informalities: The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See page 15 of the specification. Appropriate correction is required.

### *Drawings*

The drawings filed on 9/26/01 have been approved.

### *Claim Rejections - 35 USC § 112, 1st paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The nucleotide sequences that encode all human 7 transmembrane receptors (h7TMRs) encompassed within the genus have not been disclosed. Based upon the prior art there is expected to be variation among the species of cDNA, which encode h7TMRs, because the sequence of h7TMRs cDNAs would be expected to vary among individuals, particularly because such nucleotide sequences encode h7TMRs having different structures and functions. See page the specification on page 3, in lines 10-17. The specification discloses the nucleotide sequences that encode 5 h7TMRs (GPR18, GPR7, HCEPR, AXPR35, and Octoray) but does not disclose the other nucleotide sequences that encode h7TMRs. There is no evidence on the record of a relationship between the structure of any h7TMR cDNA and the 7TMR cDNAs embraced by the claims that would provide any reliable information about the structure of other 7TMR cDNAs within the genus. There is no evidence on the record that the disclosed human 7TMR cDNAs had a known structural relationship to any other 7TMR cDNA sequences; the art indicated that there is variation between 7TMR cDNA sequences. There is no evidence of record that would indicate that the nucleotide sequences encoding 7TMRs embraced by the claims when expressed in the context of a transgenic C. elegans would result in the appearance of a known phenotype such as exploded (Exp), dumpy (Dpy), long body (Lon), hyperactive movement (Hpr), paralyzed (Prl), molt defect (mlt), sterile (Ste), sick (Sck), body morphology defect (Bmd), vuvlaless (Vul), slow growth (Gro), egg laying defect (Egl), larval arrest (Lva), larval lethal (Let), protruding vulva (Pvl), multiple vulva (Muv), sterile progeny (Stp), small (Sma), clear (Clr), blistered (Bli),

high incidence of male progeny (Him), roller (Rol), larval lethal (Lvl), uncoordinated (Unc), or embryonic lethal (Emb). It is noted that the specification has disclosed that expression of GPR18, GPR7, HCEPR, AXOR35, and Octoray in a transgenic C. elegans resulted in a phenotype of egg-laying defect (Egl).

In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by member of the genus, because the disclosed cDNA sequences are not representative of the genus of cDNA sequences encoding 7TMRs embraced by the claims. Consequently, since Applicant was in possession of only the disclosed cDNAs and since the art recognized variation among the species of the genus of cDNAs that encode7TMRs, the disclosed cDNAs are not representative of the genus of nucleotide sequences encoding 7TMRs embraced by the claims. Therefore, Applicant was not in possession of the genus of 7TMR cDNAs as encompassed by the claims. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Claims 1-3 and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a transgenic *C. elegans* that expresses a human 7TMR pan-neuronally. The claims are further directed to methods of making and using the same.

The specification has discussed that the instant invention features transgenic *C. elegans* that express human 7-transmembrane receptors (7TMRs). See pages 1-2. The specification has contemplated that such transgenic *C. elegans* can be used to identify substances that affect 7TMRs. While the specification, on pages 37-38, has provided guidance and working examples that correlate to the creation of five transgenic *C. elegans* whose genomes comprise different genes encoding different h7TMRs (GPR18, GPR7, HCEOR, AXOR35, and Octoray) respectively wherein the transgenic *C. elegans* exhibit a phenotype of egg laying defect (egl), the specification has not provided guidance which correlates to the creation of the other transgenic *C. elegans* and their resulting phenotypes embraced by the claims. Moreover, the claims embrace twenty-five known phenotypes exhibited by *C. elegans*. The specification has contemplated that these known phenotypes may correlate to expression of h7TMRs in transgenic *C. elegans*. The specification however, has failed to correlate phenotypes other than egl with expression of h7TMRs (as mentioned previously)

in transgenic *C. elegans*. Further, the specification has failed to provide guidance that correlates said known phenotypes with a known disease or disorder, such that said transgenic *C. elegans* serves as a disease model, wherein methods of identifying substances that affect h7TMRs could result in identification of a substance that ameliorates a phenotype associated with the disease or disorder. As such the instant specification has failed to teach how to use said transgenic *C. elegans*. In view of the lack of guidance provided by the instant specification it would have required undue experimentation to make and use the invention as claimed.

As a first issue the claims embrace transgenic *C. elegans* that express an h7TMR pan-neuronally, wherein said *C. elegans* exhibits a known phenotype. The specification has disclosed twenty-five known phenotypes of *C. elegans* (see page 4) which may correlate to expression of an h7TMR. However, given the state of the art of transgenesis it does not appear possible to predict a phenotype resulting from expression of an h7TMR in a *C. elegans*. Applicant's response to the restriction requirement supports the Examiner's position regarding the unpredictability of phenotypes. Applicants have appear to have conceded that a phenotype resulting from expression of a transgene is unpredictable by stating that "expression of a human 7TM receptor pan-neuronally does not ensure that any one phenotype, or combination of phenotypes, will be exhibited by the *C. elegans* that is expressing the 7TM receptor. In addition, any phenotypes found in the *C. elegans* cannot be predicted in advance, and indeed are not important for the application of the invention". See page 2 of the response. In general, the

transgenic art has set forth that the phenotypic unpredictability correlates to levels of transgene expression, site of transgene integration into the genome, the transgene sequences, particularly the protein product encoded by the transgene, and the promoter sequence contained within the transgene. In addition to the preceding issues, there appears to exist another level of complexity associated with expression of vertebrate genes in invertebrates such as *C. elegans* that adds to the unpredictability of transgene expression. Link et al (Mechanisms of Ageing and Development, 2001, 122: 1639-1649) has reported on the state of transgenic invertebrate models of human age-associated neurodegenerative disease. Link et al discusses that some of the transgenic models are insufficient as disease models do to poor transgene expression. Link et al goes on to suggest "a failure to replicate in some way disease pathology in an invertebrate model may indicate, "the toxic mechanism is vertebrate specific, or might simply result from a technical hurdle". It appears that expression of human transgenes resulting in a phenotype (toxic mechanism) may be inhibited in invertebrates, such as *C. elegans*. In light of the above reasoning, it appears that the specification has not provided guidance which overcomes the phenotypic unpredictability resulting from expression of a transgene such that the skilled artisan could predict that pan-neuronal expression of an h7TMR could result in a known phenotype (consistent with the discussions of the specification). The working examples provided by the instant specification correlate the expression of 5 h7TMRs (GPR18, GPR7, HCEPR, AXOR35, and octoray) respectively, in the context of a transgenic C. elegans, with a phenotype of egl, but do not

support the breadth of the claims with respect to phenotype and h7TMR. The working examples however do not correlate any other phenotype with expression of any other 7hTMR. According it appears that the specification has failed to provide guidance, which correlates other phenotype/7TMR combinations. Given the lack of guidance provided by the specification it would have required undue experimentation to make and use the invention as claimed.

As a final issue, given the failure of the specification to correlate any of the disclosed known phenotypes with a known disease or disorder it appears that the specification has failed to teach how to use the transgenic *C. elegans* embraced by the claims. A failure to correlate the disclosed known phenotypes with a known disorder or disease implies that such transgenic *C. elegans* cannot serve as disease models, wherein they could be used for screening substances to identify a substance, which ameliorates a disease phenotype or symptom. The specification has contemplated that the transgenic *C. elegans* may be used in such a capacity. However, the specification has not provided any other uses for the transgenic *C. elegans* embraced by the instant claims. As such the specification has not provided any uses such C. elegans that are enabled. Accordingly, given the lack of guidance provided by the instant specification the skilled artisan would not know how to use the transgenic *C. elegans* embraced by the claims.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the production of transgenic *C. elegans* comprising a gene encoding a h7TMR, the lack of direction or guidance

provided by the specification for the production of transgenic *C. elegans* comprising a gene encoding a h7TMR, the absence of working examples for the demonstration or correlation to the production of a transgenic *C. elegans* comprising a gene encoding a h7TMR that exhibits a phenotype other than those exemplified, the unpredictable state of the art with respect to a phenotype that results from expression of a human transgene in a *C. elegans*, and the breadth of the claim drawn to all transgenic *C. elegans* expressing all h7TMRs, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

**Conclusion**

**No claim is allowed.**

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

Peter Paras, Jr.

Art Unit 1632

PETER PARAS
PATENT EXAMINER